PATENT SPECIFICATION (11) 1 561 504

1 561 504

(21) Application No. 32335/76 (22) Filed 3 Aug. 1976
(61) Patent of Addition to No. 1 445 524 dated 30 Jan. 1974
(31) Convention Application No. 7 524 486
(32) Filed 6 Aug. 1975 in
(33) France (FR)
(44) Complete Specification published 20 Feb. 1980
(51) INT CL³ C07D 495/04; A61K 31/54 (C07D 495/04, 221/00, 333/00)
(52) Index at acceptance
C2C 1494 1510 151X 200 213 214 215 220 226 22Y 246 247 253 254 256 25Y 28X 290 29X 29Y 30Y 313 31Y 326 337 338 360 361 362 366 367 368 36Y 37X 43X 623 628 62Y 652 65X 666 668 68Y 699 69Y 73Y 770 777 778 77X 802 80Y AA BC NR WC ZD ZF

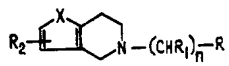
(72) Inventor ARMAND AMSELEM

(19)

(54) NEW THIENOPYRIDINE DERIVATIVES, AND THEIR APPLICATION

(71) We, CENTRE D'ETUDES POUR L'INDUSTRIE PHARMACEUTIQUE, a French Body Corporate of 195, Route d'Espagne, 31 023 Toulouse, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

In our British Patent 1445524, we claim *inter alia* tetrahydrothieno[3,2-c]-pyridine derivatives having the following formula:

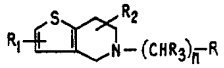


in which X represents oxygen or sulphur; R represents a phenyl radical optionally substituted with at least one halogen atom or hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or sulfonylamino group; R_1 represents a hydrogen atom or a hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, nitro or amino group; R_2 represents a hydrogen or halogen atom and *n* is zero or an integer of from 1 to 15; and in which the symbols R_1 may have different meanings in each radical CHR_3 when *n* is greater than 1,

and their inorganic or organic acid addition salts and quaternary ammonium derivatives.

We have now discovered new derivatives of the type disclosed in the above patent which also exhibit valuable therapeutic properties, particularly inhibitor action on blood-platelet aggregation and anti-inflammatory and vasodilator properties.

Thus, the present invention provides pyridine derivatives having the formula:



(I)

in which:

R is a phenyl group substituted with at least one phenyl, carboxy, alkoxy-carbonyl, cyano, hydroxymethyl or methylenedioxy group, or a styryl, thienyl or benzhydryl radical optionally substituted with at least one halogen atom or C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, nitro, amino, sulfonylamino, carboxy, alkoxycarbonyl, cyano, hydroxymethyl or methylenedioxy group;

R_1 and R_2 each represent at least one hydrogen or halogen atom or hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, nitro or amino group;

R_3 represents a hydrogen or halogen atom or a hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, nitro or amino group; and

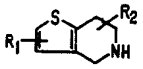
n is an integer of from 1 to 15; and

in which R_3 may have different meanings in each CHR_3 group when n is greater than 1,

and their inorganic or organic acid addition salts and quaternary ammonium derivatives.

The compounds of this invention may be prepared according to the method disclosed in our Specification 1445524.

They may also be prepared by a process comprising condensing a tetrahydrothienopyridine of the formula:



(II)

in which R_1 and R_2 have the above-defined meanings, with a halogen derivative of the formula:

$$X—(CHR_3)_n—R \qquad \text{(III)}$$

in which X is a halogen atom, and R, R_3 and n have the above-defined meanings, and then, when an ester group is present in the product, if desired hydrolysing or reducing the ester group to form other compounds of formula (I).

The condensation reaction is conducted in an inert solvent medium such as dimethylformamide, acetonitrile, dioxan or toluene.

The following Examples illustrate the preparation of the compounds of this invention.

EXAMPLE 1.

5-o-Methoxycarbonylbenzyl-4,5,6,7-tetrahydro-thienyl[3,2-c]pyridine (Derivative n°1)

A mixture of thieno[3,2-c]pyridine (3.77 g; 27.8 mmoles), o-methoxycarbonylbenzyl bromide (6.7 g; 29.3 mmoles) and acetonitrile (40 cc) is refluxed for 4 hours. The precipitate obtained on cooling is filtered off, washed with ether and recrystallized from isopropanol (M.p.=191°C. Yield: 84%).

To a solution of the above compound (35.8 g; 97.2 mmoles) in water (100 cc) and ethanol (400 cc) is added portionwise, and while cooling with an ice-bath, 7.5 g sodium borohydride. After stirring overnight at room temperature, the excess borohydride is destroyed by addition of acetone. The resulting material is concentrated *in vacuo* and the residue is extracted with ether. The organic extracts are washed with water, dried over sodium sulfate and concentrated *in vacuo*. An equivalent amount of maleic acid in ethanol solution is added to the resulting residual oil of the title compound. The maleate thus obtained is filtered off, washed with ether and recrystallized from isopropanol (M.p. = 155°C. Yield: 77%).

EXAMPLE 2.

5-*o*-Carboxybenzyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (Derivative n°2)

A mixture of 5-*o*-methyoxycarbonylbenzyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Derivative n°1; 19 g; 66 mmoles), ethanol (200 cc) and NaOH (20 cc; d=1.38) is refluxed for one hour. After cooling, the mixture is accurately neutralized with 6N hydrochloric acid and evaporated to dryness. The solid residue is washed repeatedly with a methylene chloride-ethanol mixture. The washing solutions are combined, dried over sodium sulfate and concentrated *in vacuo*. The residue is recrystallized from ethanol. (M.p.=200—205°C. Yield: 42%).

EXAMPLE 3.

5-*o*-Methoxycarbonylbenzyl-6-methyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Derivative n°3)

A mixture of 6-methyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine hydrochloride (7.05 g; 37.2 mmoles), *o*-methoxycarbonylbenzyl bromide (9 g; 39.3 mmoles) and sodium carbonate (6.05 g; 57 mmoles) in dimethylformamide (100 cc) is stirred for 3 hours at 80°C. After cooling, the inorganic salts are filtered off and the filtrate is evaporated to dryness. The residue is dissolved in ether and the ether solution is washed with water and dried over sodium sulfate, after which the ether is evaporated off. The resulting title compound obtained as a yellow oil is treated with an equivalent amount of hydrogen chloride gas in ether solution. The

hydrochloride is filtered off and recrystallized from isopropyl alcohol-diisopropyl ether (M.p.=166°C. Yield: 53%).

EXAMPLES 4—10.

The following compounds were prepared by a procedure analogous to that described in Example 3.

Derivative n°4: 5 - [(5 - Chloro - 2 - thienyl) - methyl] - 4,5,6,7 - tetrahydro-thieno[3,2-c]pyridine hydrochloride.
White crystals. M.p.=200°C.

Derivative n°5: 5 - [2 - hydroxy - 2 - (2 - thienyl) - ethyl] - 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine fumarate.
White crystals. M.p.=150°C.

Derivative n°6: 5 - (3 - *o* - chlorophenyl - 2 - propenyl) - 4,5,6,7 - tetrahydro-thieno[3,2-c]pyridine hydrochloride.
Beige crystal. Mp = 176°C.

Derivative n°7: 5 - *o* - cyanobenzyl-4,5,6,7 - tetrahydro - thieno[3,2-c]-pyridine maleate.
Pale yellow crystals. M.p.=194°C.

Derivative n°8: 5 - (3,4 - methylenedioxy - benzyl) - 4,5,6,7 - tetrahydro-thieno[3,2-c]pyridine hydrochloride.
White crystals. M.p.=230—235°C.

Derivative n°9: 5 - [2 - (4 - bisphenyl) - 2 - hydroxy - ethyl] - 4,5,6,7 - tetrahydro-thieno[3,2-c]pyridine hydrochloride.
White crystals. M.p.=200—210°C.

Derivative n°10: 5 - *o* - hydroxy - methylbenzyl - 4,5,6,7 - tetrahydro - thieno-[3,2-c]pyridine.
Pale cream crystals. M.p.=88°C.

The results of toxicological and pharmacological tests reported below demonstrate the useful activities of the derivatives of the present invention, particularly their inhibitor activity on blood-platelet aggregation and their anti-inflammatory and vasodilator activities.

Thus, the invention also includes a therapeutic composition, having in particular anti-inflammatory and vasodilator activities and inhibitor action on blood-platelet aggregation, comprising, as active ingredient, a compound of the formula (I) or a pharmaceutically acceptable acid addition salt or quaternary ammonium derivative thereof together with a pharmaceutically acceptable carrier.

TOXICOLOGICAL INVESTIGATION

Said investigation demonstrated the low toxicity and the good tolerance of the compounds of the invention.

For indicative purposes, the LD_{50}/24 hrs/kg body weight of the animal, determined in mice by the intravenous route, is 92 mg for derivative n° 1, 300 mg for derivative n°2, 65 mg for derivative n°3, 165 mg for derivative n°4, 75 mg for derivative n°5, 60 mg for derivative n°6, 45 mg for derivative n°7 and 65 mg for derivative n°8.

PHARMACOLOGICAL INVESTIGATION

1. *Anti-inflammatory action*

Said action was investigated according to two methods.

(a) *Localised carrageenin-induced edema method:*

A 1% carrageenin solution (0.1 ml) is injected in the metatarsal flexor muscles of the right hind limb of rats at time 0.

The animals of the treated group are additionally given orally 100 mg/kg of the test compound, first one hour prior to and then simultaneously with the injection of the phlogogenic agent, and then one hour and 2.5 hrs thereafter. The percent anti-inflammatory activity with reference to the reference group, as a function of time, is determined by measurements taken with a Roch micrometer at times 0, one hour, two hours, three hours and five hours after carrageenin administration. The results obtained with derivatives n° 1, 4, 5, 8 and 10 are set forth in the following Table.

Derivative N°.	Percent anti-inflammatory activity		
	after 1 hour	after 2 hours	after 5 hours
1	43	50	55
4	39	47	54
5	45	53	59
8	41	51	59
10	36	48	56

(b) *Ovalbumin-induced systemic edema method*

Rats are given a simultaneous intraperitoneal injection of 1 ml ovalbumin and 0.5 ml of a 1% aqueous Evans Blue solution. The animals of the treated group are additionally given orally 100 mg of the test compound both 1 hr prior to and simultaneously with ovalbumin administration. The intensity of the phenomenon thus induced is scored according to a scale of 1 to 5, according to the progress of the inflammatory syndrome. Thus the mean intensity of the edema and the percent decrease of the edema reaction with respect to the control group are determined. Said percentages are set out in the following Table:

Derivative N°.	Percent decrease	
	after 2 hours	after 3 hours
1	51	58
4	48	53
5	50	61
8	54	64
10	51	62

2. *Inhibitor action on blood-platelet aggregation*

The normally cloudy blood-platelet-rich serum of rats is made clear by addition of adenosine diphosphate, which induces aggregation of the blood-platelets. When the same test is made on serum taken from an animal to which has been administered 100 mg/kg of a compound having an inhibitor effect on blood-platelet aggregation, there is no aggregation of the blood-platelets and the serum remains cloudy. Thus, the inhibitor action on blood-platelet aggregation of the test derivatives may be evaluated by means of a simple spectrophotometric turbidimetric assay.

The tests carried out with groups of five rats (three controls and 2 treated animals) show that the derivatives of the present invention possess substantial activity and protect the test animals against blood-platelet aggregation in a ratio of the order of 95%.

3. *Peripheral and cerebral vasodilator action*

This investigation, carried out in rabbits, demonstrated the marked vasodilator action of the compounds of the invention.

Indeed, administration (perfusion) to the test animals of a solution containing 10 mg/ml per minute, over 20 minutes, produces a substantial vasodilation of the cerebral blood vessels. Indeed, the rheographic investigation demonstrated a marked increase of the cerebral rate of flow associated with a decrease of the peripheral vascular resistance.

It is apparent from the toxicological and pharmacological investigations reported above that the compounds according to the present invention have a good tolerance and possess anti-inflammatory and vasodilator activities and inhibitor action on blood-platelet aggregation.

The therapeutic compositions of the present invention may be formulated for oral administration as tablets, coated tablets, capsules, drops or syrups. They may also be formulated as suppositories for rectal administration, and as injectable solutions for parenteral administration.

Each unit dose preferably contains from 0.025 g of 0.500 g active ingredient, the daily dosage regimen varying within the range from 0.025 g to 1 g active ingredient.

Examples of pharmaceutical formulations of the therapeutic compositions of this invention are given below.

EXAMPLE 11.

Tablets

Derivative n°2	0.150 g
Polyvinylpyrrolidone	0.010 g
Magnesium stearate	0.005 g
Starch	0.010 g
Lactose	0.025 g

EXAMPLE 12

Coated tablets

CORE	Derivative n°5	0.100 g
	Magnesium stearate	0.010 g
	Kaolin	0.005 g
	Rice starch	0.020 g
	Lactose	0.015 g
COATING	Silica	0.005 g
	Gum arabic	0.003 g
	Gelatin	0.005 g
	Talc	0.010 g
	White wax	0.002 g
	Titanium dioxide	0.001 g
	Tartrazine yellow	traces
	Officinal white sugar, sufficient for 1 coated tablet	

EXAMPLE 13.

Capsules

Derivative n°6	0.150 g
Magnesium stearate	0.005 g
Starch	0.010 g

EXAMPLE 14.

Drops

Derivative n°7	1.5 g
Flavoured excipient, sufficient to make	30 ml

EXAMPLE 15.

Suppositories

Derivative n°9	0.125 g
Semi-synthetic triglycerides, sufficient to make	1 suppository

EXAMPLE 16.

Injectable solution

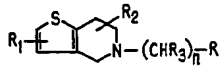
Derivative n° 10	0.100 g
Isotonic solution, sufficient to make	3 ml

In view of their anti-inflammatory, vasodilator and blood-platelet aggregation inhibitor properties, the therapeutic compositions of the invention are usefully for therapeutic purposes. In short or extended treatments, they are applicable to inflammatory reactions to decrease edema, hypersecretion and exudation and to prevent the occurrence of the inflammatory lesion. They are indicated in the treatment of post-trauma or post-surgical edema, in plastic surgery, in stomatological surgery, in the treatment of conditions associated with inflammatory reactions (e.g. angina and bronchitis), in inflammatory or degenerative rheumatism and in acute subarticular conditions.

In addition, in view of their inhibitor effects on blood-platelet aggregation and of their vasodilator effects they are advantageous in the treatment of cardiovascular conditions, both for curative and for preventive purposes; they have a favourable effect in the treatment of disorders of the cerebral and peripheral circulatory system and prevent thrombosis-forming complications of atheroma.

WHAT WE CLAIM IS:—

1. Pyridine derivatives having the formula:



(I)

in which:

R is a phenyl group substituted with at least one phenyl, carboxy, alkoxycarbonyl, cyano, hydroxymethyl or methylenedioxy group, or a styryl, thienyl or benzhydryl radical optionally substituted with at least one halogen atom or C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, nitro, amino, sulfonylamino, carboxy, alkoxycarbonyl, cyano, hydroxymethyl or methylenedioxy group;

R_1 and R_2 each represent at least one hydrogen or halogen atom or hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, nitro or amino group;

R_3 represents a hydrogen or halogen atom or a hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, nitro or amino group; and

n is an integer of from 1 to 15; and

in which R_3 may have different meanings in each CHR_3 group when n is greater than 1,

and their inorganic or organic acid addition salts and quaternary ammonium derivatives.

2. 5-*o*-Cyanobenzyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and the pharmaceutically acceptable acid addition salts and quaternary ammonium derivatives thereof.

3. Compounds as claimed in claim 1, said compounds being substantially as described in any one of Examples 1 to 10.

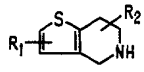
4. A therapeutic composition comprising, as active ingredient, a compound as claimed in claim 1 or a pharmaceutically acceptable acid addition salt or quaternary ammonium derivative thereof, together with a pharmaceutically acceptable carrier.

5. A composition as claimed in claim 4 which is in unit dosage form, each unit dose containing 0.025—0.500 g active ingredient.

6. A composition as claimed in claim 4 or claim 5 wherein the active ingredient is the compound claimed in claim 2.

7. A therapeutic composition as claimed in claim 4 substantially as described in Examples 11 to 16.

8. A process for the preparation of a compound as claimed in claim 1, which comprises condensing a compound of the formula



(II)

(where R_1 and R_2 are as defined in claim 1) with a compound of the formula $X—(CHR_3)_n—R$ (where X is a halogen atom and R, R_3 and n are as defined in claim 1).

9. A process as claimed in claim 8 wherein the compound prepared contains an ester group, and the ester group is then hydrolysed or reduced to form other compounds as claimed in claim 1.

FRANK B. DEHN & CO.,
Imperial House,
15—19 Kingsway, London, WC2B 6UZ.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1980.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.